REMARKS

The Examiner has maintained his rejection of Claims 1 and 2 under 35 U.S.C. 103(a) as being allegedly unpatentable over Sims (U.S. Patent No. 5,288,507) in view of Stuerzebecher (U.S. Patent No. 5,523,321) and further in view of Kararli et al (U.S. Patent No. 5,935,939. Respectfully applicant with his prior response setout clearly the lack of motivation to one skilled in the art in each individual reference to combine with the other references suggested by the Examiner. The motivation is not present in the teaching of the references alone or in combination nor is any suggestion present in any of the references to one skilled in the art as to the possibility or suggestion that they can be combined and further that such a combination would result at the invention as defined in the claim set. Clearly, the prior art does not suggest or provide any reason or motivation to make such a modification as purported by the Examiner.

The following represents excerpts from the Declaration of Dr. Michael Lipp which are representative of his opinions, that is of one who is an expert in his field which respectfully the Examiner is not. The Examiner is referred to the CV of Dr. to support this fact. In his Declaration at paragraph 4 he states :

"In my opinion, the inventions described in claims 1 through 11 set out in the '142 patent application are **not** obvious in light of the teachings and disclosures of U.S. Patent No. 5,288,507 (hereafter referred to as the '507 patent) in view of U.S. Patent No. 5,523,321 (hereafter referred to as the '321 patent) and U.S. Patent No. 5,935,939 (hereafter referred to as the '939 patent) and also are **not** obvious in light of the teachings and disclosures of U.S. Patent No. 5,232,704 (hereafter referred to as the '704 patent) in view of the '321 patent. I thus disagree with the conclusions reached by the Examiner the Final Action with respect to the '142 patent application. I describe my opinions further below, beginning with a summary of the claimed inventions in question of the '142 patent application followed by my opinion with respect to the Examiner's comments and conclusions concerning the teachings and claimed inventions of the '507, '329, '939 and '704 patents."

With reference to In Re: Regal, 526 F. 2d 1399, 1403 n. 6, 188 USPQ 136, 139 n. 6 (CCPA 1975).

> "There must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references".

Therefore, it is Applicant's view and that of Dr. Lipp as well, that there is no evidence of motivation in the prior art, either within the references themselves, or knowledge generally available to one of ordinary skill in the art, to make the purported changes suggested by the Examiner to arrive at the claimed subject matter. Nothing within the Examiner's purported combination of Sims, Kararli and '321 reference teaches Applicant's invention as set out in Claim 1. The combination falls well short and at best if made might include if the Examiner's logic were use (with no admission being made that such logic is acceptable in law or correct) granules of an active which may be a prostaglandin and an NSAID. However such a combination falls well short of Applicant's invention namely:

> A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet, being protected by said shell.

The Examiner is referred to the arguments setout below in greater detail and those in the Declaration of Dr. Lipp at the referenced paragraph which are representative of his opinions, that is of one who is an expert in his field which respectfully the Examiner is not. The Examiner is referred to the CV of Dr. to support this fact.

In paragraph 7 *The solution to these issues related to misoprostol chemical stability captured in the inventions of the '142 patent application involves the development of a novel combination tablet formulation that serves to protect and isolate the misoprostol incorporated therein from both the NSAID and the tablet surface. This novel combination tablet formulation is comprised of individual, pharmaceutically acceptable tablets (two total) containing the NSAID (tablet 1) and misoprostol (tablet 2, with both tablets containing additional excipients as standardly included in tablet formulations) embedded in a single larger combination tablet via compression in the presence of an additional excipient or mixture of excipients which serves to form a shell around the individual single-drug tablets. This excipient shell serves both to separate the embedded NSAID tablet from the embedded misoprostol tablet and to prevent exposure of the misoprostol tablet to the surface of the*

combination tablet. As a result, the probability of the occurrence of deleterious chemical reactions between misoprostol and the NSAID or between misoprostol and water or oxygen at the tablet surface is greatly reduced.

In paragraph 17 *Thus, in my opinion, by effectively decoupling the processing of formulations containing an NSAID and misoprostol via (1) the formation of two separate small tablets containing the individual drugs and then (2) the combining of these two smaller tablets into a single combination tablet with a protective shell of excipient via simple compression in the dry state in a tablet press as described above, the inventors of the '142 patent circumvent the known instability issues related to misoprostol in the presence of an NSAID without requiring (i) the use of complex manufacturing equipment or costly unit operation steps such as multiple core coating steps, (ii) the formation of granules via wet granulation, (iii) the formation of an amorphous dispersion of misoprostol with excipient, or any other process that would increase the cost or manufacturing complexity of combination tablet production.*

In paragraph 22 *As I describe below, I disagree with the Examiner's conclusions regarding the combined teachings of the '507, 321 and '939 patents summarized above. In my opinion, these three patents, read alone or in combination, do not render the inventions of the '142 patent obvious. Further, it is also my opinion that these three patents (i) in part teach away from each other and thus should not be read together (ii) do not make obvious the inventions of the '142 patent application and (iii) in fact teach away from the inventions of the '142 patent application. For similar reasons, I would not expect that a skilled formulator would have been motivated to follow the combined teachings of these three patents when trying to develop a stabilized combination tablet formulation containing a NSAID and misoprostol. I first review the pertinent information disclosed in each of these three patents then provide my opinions concerning their combined teachings.*

In paragraph 38 *I disagree with this position taken by the Examiner for a number of reasons. In general, I am not aware of granules arising from a standard wet granulation process as being considered to be or called tablets in any of the standard pharmaceutical texts concerning tablet formulation that I have encountered. As described in Chapter 37 (entitled "Granulation") of the reference edited by M. Aulton entitled*

"Pharmaceutics: The Science of Dosage Form Design" submitted for consideration by Counsel for the inventor of the '142 patent (the "Churchill/Livingston" reference, included as Exhibit F to this my Declaration), with respect to tablet formulation and tablets in general, granules produced by either wet or dry granulation processes are considered precursors to tablets and are not considered to be tablets themselves in any sense. For example, it is stated on page 616 of Exhibit F that:

> *"**Granulation is the process in which powder particles are made to adhere to form larger particles called granules. In the majority of cases this will be undertaken in the production of tablets or capsules, when granules will be made as an intermediate product**, but granules may also be used as a dosage form (see Chapter 17). Granulation will commence after mixing the necessary powdered ingredients so that a uniform distribution of each ingredient through the mix is achieved. **After granulation, the granules will be packed when used as a dosage form or they may be mixed with other excipients prior to tablet compression or capsule filling."***
> *(Emphasis added.)*

In paragraph 39 *In my opinion, there are several other reasons as to why such granules are not considered to be tablets themselves. Tablets are generally and widely understood to be pharmaceutical dosage formulations that are required to possess a number of properties. For a given formulation, they are designed to contain a precise and reproducible amount of a drug or a combination of drugs. As described in Exhibit F and also described in other standard textbooks on tabletting technology, conventionally-produced granulations from both wet and dry processes standardly consist of a wide distribution of particle sizes. For example, it is stated on page 621 of Exhibit F that:*

> *"Nuclei can grow by two possible mechanisms: either single particles can be added to the nuclei by pendular bridges or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed.*
>
> ***This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that the size distribution is not excessively large, this point represents a suitable end-point for granules used in capsule and tablet manufacture as relatively small granules will produce a uniform***

tablet die or capsule fill. *Larger granules may give rise to problems in small diameter dies due to bridging across the die and uneven fill." (Emphasis added.)*

Thus, granules so produced would not be considered to be pharmaceutical tablets due to the wide distribution in sizes and resulting drug contents of the granules. Additionally, as indicated in the passage above from Exhibit F, the mean or median geometric diameter of the granules so produced is typically significantly smaller than the typical diameter of a pharmaceutical tablet.

In paragraph 50 *As I have indicated above, upon my review of the '507, '321 and '939 patents, I have not found any disclosures or information in these patents that teaches toward or makes obvious the claimed inventions of the '142 patent application. It is also my opinion that the combined disclosures of these three patents, when read together, do not teach towards or make obvious the claimed inventions of the '142 patent application. In my opinion, the combined teachings of these patents does not make obvious or teach towards a combination tablet formulation comprised of a smaller tablet containing misoprostol and a smaller tablet containing a NSAID surrounded by a shell of excipient which prevents exposure of the misoprostol contained therein to either the NSAID or the surface of the tablet.*

In paragraph 55 *In summary, I have not found any information or disclosures in the combined teachings of the '507, '321 and '949 patents that makes obvious the claimed inventions of the '142 patent application, and, in particular, Claims 1 and 2 of the '142 patent application.*

The Examiner has also maintained his rejection of Claims 1 to 11 under 35 U.S.C. 103(a) as being allegedly unpatentable over Franz et al. (U.S. Patent No. 5,232,704) in view of Stuerzebecher (U.S. Patent No. 5,523,321). Respectfully applicant with his prior response and in the present submission including the Declaration of Dr. Lipp has setout clearly the lack of motivation to one skilled in the art in each individual reference to combine with the other references suggested by the Examiner. The motivation is not present in the teaching of the references alone or in combination nor is any suggestion present in any of the references to one skilled in the art as to the possibility or suggestion that they can be combined and further

that such a combination would result at the invention as defined in the claim set. Clearly, the prior art does not suggest or provide any reason or motivation to make such a modification as purported by the Examiner.

The Examiner is referred to the arguments setout below in greater detail and those in the Declaration of Dr. Lipp at the referenced paragraph which are representative of his opinions, that is of one who is an expert in his field .

At paragraph 57 *As I describe further below, I also disagree with the examiners conclusions regarding the combined teachings of the '704 and '321 patents. In my opinion, these two patents, read alone or in combination, do not render the inventions of the '142 patent obvious. Further, it is also my opinion that these two patents (i) also teach away from each other and thus should not be read together and (ii) teach away from the inventions of the '142 patent application. Thus, I would not expect that a skilled formulator would have been motivated to follow the combined teachings of these two patents when trying to develop a stabilized combination tablet formulation containing a NSAID and misoprostol.*

With reference to In Re: Regal, 526 F. 2d 1399, 1403 n. 6, 188 USPQ 136, 139 n. 6 (CCPA 1975).

> "There must be some logical reason apparent from positive, concrete evidence of record which justifies a combination of primary and secondary references".

Therefore, it Applicant's view there is no evidence of motivation in the prior art, either within the references themselves, or knowledge generally available to one of ordinary skill in the art, to make the purported changes suggested by the Examiner to arrive at the claimed subject matter. Since neither Franz nor '321 teach two separate smaller tablets in a pharmaceutical tablet even if the term "granules" were read in the manner alleged by the Examiner, and for the reasons set out above this is clearly not the case, one would still not arrive at Applicant's teaching and Claim 1 as follows:

> **A pharmaceutical tablet** comprising a shell in which is imbedded **two smaller tablets** covered by the material of the shell of the pharmaceutical tablet, **one of which smaller tablets comprises an NSAID** and **the other of which smaller tablets comprises misoprostol,** whereby the two smaller tablets are not exposed

> to the environment [of] at the surface of the pharmaceutical tablet , being protected by said shell.(emphasis added)

Again respectfully the Examiner is attempting to create a 20/20 hindsight reconstruction but has fallen well short in doing so. The Examiner is referred to the arguments setout below in greater detail.

Referring now to United States Patent No. 5,288,507 hereinafter referred to as Sims, there is taught a combination of an anti-inflammatory and particularly (S)-ibuprofen being substantially free of the (R)-ibuprofen isomer, plus in one alternative embodiment it is mentioned at column 4, line 61 onward that an antiulcerative agent might be used such as misoprostol or the like. The invention may take the form of tablets and the active may be admixed with pharmaceutically acceptable diluents such as lactose, starch, sucrose, and a host of other items listed at column 5, line 5 onwards. There is however, no discussion within the Sims reference to provide the invention as defined in Applicant's claim 1.

> A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet, being protected by said shell.

There is no discussion within Sims of a pharmaceutical tablet which includes a shell in which is embedded two smaller tablets, one of which is an NSAID and one of which is misoprostol. There is no motivation within Sims to do so, and clearly with the Examiner's own admission in the action dated March 4, 2002, there is apparently no teaching in the direction of Applicant's claim 1, otherwise the Examiner would have stated such.

Referring now to Kararli, United States Patent No. 5,935,939 there is taught a stabilized dispersion of misoprostol using amorphous excipients resulting in a stable solid state amorphous dispersion of misoprostol and the excipient. Fundamentally therefore, the Kararli patent teaches a need to stabilize a misoprostol, in that prostaglandins are difficult to formulate into stable pharmaceutical dosage forms because of their relative instability. The '939 patent therefore has added to the state of the art, one way of stabilizing the misoprostol. Clearly there is nothing within Kararli other than the fact that the dispersions can be used in

the production of tablets as in Example 1 wherein they are ground using a mortar and pestle and then milled. But Kararli is silent with regard to how the dispersion might be utilized in tablet form other than that it may be utilized in a tablet form.

However, there is nothing within Kararli that teaches anything but a stable solid state amorphous dispersion of mistoprostol with an excipient selected from a certain group of excipients as set out in Claim 1. There is clearly nothing within the Kararli reference that teaches Applicant's invention as specified in Claim 1 as follows.

> A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet , being protected by said shell.

Referring now to United States Patent No. 5,523,321 to Stuerzebecher there is taught combination products containing a prostaglandin and a thromboxane receptor antagonist suitable for joint application to thrombotic and thromboembolic syndromes.

This patent therefore is silent with regard to the use of NSAIDs; it is further silent with regard to the use of mistoprostol. The primary problem being dealt with in the '321 patent is coronary heart diseases, coronary thrombosis, or the like as listed at column 1, lines 17 onward, for the inhibition of blood platelet aggregation. The combination product when given orally, may be in the form of a tablet which can be produced in "the usual way" as stated at column 4, line 34; and column 4, line 53.

Referring now to Example 1, clearly the components 3, 4 and 5 are sifted, mixed and granulated with the solution of item 1 in example 1 which is Iloprost in 50% ethanol. The term granulating therefore, clearly refers to wet granulating and that is to say the formulation of granules from particles of items 3, 4 and 5, lactose, cornstarch and polyvinylpyrrolidone 2500 which granules are subsequently dried and mixed with items 2 and 6 prior to molding into rounded tablets. Clearly, granules are therefore produced. However, respectfully the Examiner has misread the term in concluding that granules are equivalent to tablets. In fact, granules are an intermediate step prior to a tableting process.

As support of what a man skilled in the art would know about of granulation, Applicant encloses herewith pages 616 to 628 of *"Pharmaceutics: The Science of Dosage Form Design"*, published by Churchill Livingstone. The Examiner is referred to the entire section, and particularly that granules may be mixed with other excipients **prior to** tablet compression. Granules may be formed by the dry granulation method or the wet granulation method. The '321 patent clearly refers in the examples only to wet granulation. As can be seen from reading the section in the Churchill Livingstone reference, which is not an extensive reference manual on granulation, granulation is not by any means a simple process and must be monitored at all times to prevent aggregation of the granules to sizes beyond that which is desired. Clearly, there is nothing within the teachings of Churchill Livingstone that agrees in any way with the Examiner's conclusion that allegedly granules are the equivalent of tablets or would render obvious the use of tablets. Applicant does not believe that a man skilled in the art would arrive at such a conclusion, only that granules are be formed by wet granulation methods which are left unspecified in example 1 of the '321 patent. As per the teachings of Churchill Livingstone granules may be provided by wet or dry granulation in various processes and are a precursor to tableting or to be used in dosage forms when gelatin capsules are being filled to form granules of predetermined size and configuration filled into these gelatin capsules.

Referering to the McGraw-Hill DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS(Fourth edition) also attached for the Examiner's information

> Tableting is defined as follows: **a punch-and-die procedure for compaction of powdered or granular solids; used for pharmaceuticals, food products fireworks, vitamins, and dyes.**

Granulate is defined as follows: **to form or crystallize into grains, granules, or small masses.**

Clearly with respect the Examiner has misread example 1 of the '321 patent and incorrectly concluded that the resulting granules of the granulating step of example 1 would "make the use of tablets in the instant invention obvious" when '312 is silent on the specifications of the granules as per Churchill Livingstone. Clearly the process used in example 1 of '321 is not specified. It is therefore unlikely that a man skilled in the art would reach such a conclusion.

A stated in the Declaration of Dr. Lipp in support of this position he states as follows at the paragraphs indicated:

In paragraph 39 *In my opinion, there are several other reasons as to why such granules are not considered to be tablets themselves. Tablets are generally and widely understood to be pharmaceutical dosage formulations that are required to possess a number of properties. For a given formulation, they are designed to contain a precise and reproducible amount of a drug or a combination of drugs. As described in Exhibit F and also described in other standard textbooks on tabletting technology, conventionally-produced granulations from both wet and dry processes standardly consist of a wide distribution of particle sizes. For example, it is stated on page 621 of Exhibit F that:*

> *"Nuclei can grow by two possible mechanisms: either single particles can be added to the nuclei by pendular bridges or two or more nuclei may combine. The combined nuclei will be reshaped by the agitation of the bed.*
>
> ***This stage is characterized by the presence of a large number of small granules with a fairly wide size distribution. Providing that the size distribution is not excessively large, this point represents a suitable end-point for granules used in capsule and tablet manufacture as relatively small granules will produce a uniform tablet die or capsule fill.*** *Larger granules may give rise to problems in small diameter dies due to bridging across the die and uneven fill." (Emphasis added.)*

Thus, granules so produced would not be considered to be pharmaceutical tablets due to the wide distribution in sizes and resulting drug contents of the granules. Additionally, as indicated in the passage above from Exhibit F, the mean or median geometric diameter of the granules so produced is typically significantly smaller than the typical diameter of a pharmaceutical tablet.

Clearly the Examiner is relying on 20/20 hindsight which is forbidden.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

> *"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the*

> *Examiner relied upon hindsight to arrive at the determination of obviousness.* ***It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious*** *(emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."*

There is nothing within the teachings of the '321 patent that would motivate one skilled in the art to somehow combine the teachings of Sims and Kararli with '321 since the problems being solved by each reference are somewhat mutually exclusive. Kararli teaches only a stabilized dispersion of misoprostol using amorphous excipients resulting in a stable solid state amorphous dispersion of misoprostol and the excipient. Sims teaches a combination of an anti-inflammatory and particularly (S)-ibuprofen being substantially free of the (R)-ibuprofen isomer, plus in one alternative embodiment an antiulcerative agent might be used such as misoprostol or the like. '321 teaches combination products containing in one embodiment a prostaglandin and a thromboxane receptor antagonist suitable for joint application to thrombotic and thromboembolic syndromes. How then would one skilled in the art of Sims be motivated to use the amorphous form of misoprostol of Kararli and even they were with no admission that this is the case why would such a combination be further combined with the teachings of '312 when clearly the problems addressed in '321 are quite different namely cardiac and cardiovascular problems. What would motivate one skilled in the art to do so. Clearly the Examiner is incorrectly picking and choosing from the prior art elements in creating a 20/20 hindsight reconstruction.

ATD Corporation v. Lydall, Inc., 48 USPQ 2d 1321, 1329 (Fed. Cir. 1998)

> Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. **There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.(emphasis added)**

Nothing within the Examiner's purported combination of Sims, Kararli and '321 reference teaches Applicant's invention as set out in Claim 1. The combination falls well short and at

best if made might include if the Examiner's logic were use (with no admission being made that such logic is acceptable in law or correct) granules of an active which may be a prostaglandin and an NSAID. However such a combination falls well short of Applicant's invention namely:

> A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet, being protected by said shell.

If one skilled in the art were to combine the teachings of Sims, the '321 reference and Kararli they would not arrive at Applicant's invention **as supported by Dr. Lipp's Declaration .** First of all, there is nothing within the '321 reference that teaches the use of two separate tablets and as taught in Applicant's disclosure that either by using dry powder or granules the two smaller tablets are formed, one containing an NSAID and the other containing misoprostol. Clearly, there is no teaching in any of the references alone and in combination to do so. Respectfully, the Examiner has created a 20/20 hindsight using the Applicant's invention as a blueprint hoping to arrive at such a combination but has respectfully fallen well short, since clearly there is no teaching within either of the three references with respect to Applicant's invention as set out in Claim 1 above, and there is no motivation from either of the references alone or in combination to arrive at Applicant's invention. The Examiner however, has incorrectly concluded that the combination is allegedly relevant having misread Stuerzebecher resulting in firstly misreading, and then misapplying the term granules from a very limited disclosure in the examples, and particularly Example 1 of Stuerzebecher. One granulates prior to tableting in many cases depending on the disintegration and release characteristics desired. How then does the Examiner reach the conclusion that Claim 1 is obvious. Clearly, this is a 20/20 hindsight reconstruction, that is to say using the term granules to render allegedly obvious the term tablets and even if this were the case, there still is no teaching in any of the three references, Sims, Stuerzebecher or Kararli alone or in combination that teaches Claim 1 as set out below.

> A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the

environment [of] at the surface of the pharmaceutical tablet , being protected by said shell.

Respectfully, the Examiner is creating a 20/20 hindsight reconstruction using Applicant's invention as a blue print to allegedly find elements of Applicant's combination in the prior art. This is not permissible as set out In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

> *To prevent the use of hindsight based on the invention to defeat patentability of the invention,* ***this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*** (emphasis added)

The following cases also review the Federal Circuits recent decisions regarding hindsight reconstruction.

In re Oetiker, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992)

> The combination of elements from non-analogous sources, in a manner that reconstructs the applicant's invention only with the benefit of hindsight, is insufficient to present a prima facie case of obviousness. **There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination.** (emphasis added)That knowledge can not come from the applicant's invention itself.

ATD Corporation v. Lydall, Inc., 48 USPQ 2d 1321, 1329 (Fed. Cir. 1998)

> Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. **There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.(emphasis added)**

Al-Site Corp. v. VSI Int'l, Inc., 50 USPQ 2d 1161, 1171 (Fed. Cir. 1999)

> VSI is unable, however, to point to any specific teaching or suggestion for making this combination. VSI instead relies on what it presumes is the level of knowledge of one of ordinary skill in the art at the time of the invention to supply the missing suggestion to combine. In the first place, the level of skill in the art is a prism or lens through which a judge or jury views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet,

hindsight, to gauge obviousness. **Rarely, however, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. . . . Skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case** (emphasis added), but instead supplies the primary guarantee of objectivity in the process.

In re Dembiczak, 50 USPQ 2d 1614, 1616-17 (Fed. Cir. 1999) (quotations omitted)

Our analysis begins in the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the tempting but forbidden zone of hindsight, when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, **guided only by the prior art references and the then-accepted wisdom in the field**. (emphasis added) Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. In this case, the Board fell into the hindsight trap. . . . The range of sources available, however, does not diminish the requirement for actual evidence. That is, **the showing must be clear and particular** (emphasis added).

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness. ***It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious*** *(emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."*

In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

"As this court has stated, "virtually all [inventions] are combinations of old elements." Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 USPQ 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents

solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 USPQ 2d 1551, 1554 (Fed. Cir. 1996).

To prevent the use of hindsight based on the invention to defeat patentability of the invention, ***this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*** (emphasis added)

This court has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. In this case, the Board relied upon none of these. Rather, just as it relied on this high level of skill in the art to overcome the differences between the claimed invention and the selected elements in the references, it relied upon the high level of skill in the art to provide the necessary motivation. The Board did not, however, explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the field of art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Because the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, ***this court infers that the examiner selected these references with the assistance of hindsight. This court forbids the use of hindsight in the selection of references that comprise the case of obviousness.*** (emphasis added)*See In re Gorman, 933 F.2d 982, 986, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen and Ruddy."*

Referring now to United States Patent No. 5,232,704 to Franz, herein referred to as '704 there is clearly taught that prostaglandins are involved in the treatment of ulcers. They inhibit gasteric secretions from the stomach parietal. The '704 reference therefore proposes to

provide a bi-layer floating dosage form to improve the delivery of the prostaglandin and particularly misoprostol to a patient. The '704 reference then goes on in the background to discuss other buoyant type floating tablets, and further in the summary of the invention clearly teaches a non-compressed bi-layer formulation, wherein one layer includes the drug release layer, and where the other is only the buoyant or floating layer, in order to ensure that substantially all of the drug is released in the stomach over the extended period of time. Gelling agents therefore are incorporated in the buoyant layer which hydrates in gasteric juices and forms a gelatinous barrier or mass which is contained in a separate layer from the drug release formulation layer. This theme is repeated throughout the detailed description of the '704 specification, and at column 4, line 4, it states,

> *"Examples of suitable NSAID's to mix or combine with a prostaglandin drug are diclofenac, piroxicam, ibuprofen or naproxen. An example of a suitable combination or mixture is diclofenac in a therapeutic amount such as from about 25 to 75 milligrams and the prostaglandin misoprostol in a therapeutic amount of from about 100 to 200 micrograms."*

Clearly, it was the intent of the '704 Franz teaching that the drugs **are mixed and combined in the one drug layer** and never in the buoyant layer. Clearly, Gimet the '225 reference teaches that this should not be done, and that a problem will result in doing so. **It is never contemplated within Franz to separate these two components since Franz did not appreciate the problem identified in the later reference Gimet '225 and addressed by Applicants invention in claim 1.** Franz was preoccupied with floatation and to ensure that the composition is buoyant in the stomach and remains in the stomach for the full period that the NSAID is being ingested. The Examiner is encouraged to re-read the specification of Franz to arrive at the conclusion and the only conclusion available, that is to say the second layer is the buoyancy layer designed for particular residence time of the composition within the stomach to ensure that the entire contents of the composition is ingested in the stomach.

In the preferred embodiment of Franz the drug release layer is filled into a capsule without any compaction using a conventional capsule filling machine and the buoyant layer is then added by free-flowing the powder mixture into the capsule body. An over-filling of the buoyant layer is used to minimize mixing of the two layers. It is further recommended that the composition be taken after ingesting a heavy meal which in turn would ensure the buoyancy or floatation of the composition in the contents of the stomach.

Clearly therefore, Franz does not even fully appreciate the problems associated with combining NSAID's and misoprostol since Franz teaches mixing of the NSAID and the prostaglandin in one layer. A man skilled in the art would not therefore follow such teaching to provide a composition containing NSAID's and misoprostol in the same layer . Surely a fair objective reading of Franz would not result in Applicant's invention, namely:

A pharmaceutical tablet comprising a shell in which is imbedded two smaller tablets covered by the material of the shell of the pharmaceutical tablet, one of which smaller tablets comprises an NSAID and the other of which smaller tablets comprises misoprostol, whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet, being protected by said shell.

Clearly, Franz does not teach two tablets contained within a pharmaceutical tablet including a shell which surrounds the two smaller tablets each containing only one of the NSAID and the misoprostol. Franz never appreciated the fact that the prostaglandin and an NSAID should not be mixed together in the same layer. He provides a second buoyant layer as admitted by the Examiner in order to provide full ingestion of the actives within the stomach.

Clearly, however, Franz did not even appreciate the need of separating the NSAID and the misoprostol as set out in Applicant's invention as follows:

> **A pharmaceutical tablet** comprising a shell in which is imbedded **two smaller tablets** covered by the material of the shell of the pharmaceutical tablet, **one of which smaller tablets comprises an NSAID** and **the other of which smaller tablets comprises misoprostol,** whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet , being protected by said shell.(emphasis added)

Referring now to any combination of Franz and Stuerzebecher '321 patent, Franz does not address the problems as set out in Applicant's disclosure, that is to say the importance of protecting misoprostol from the environment and from the NSAID separately. Clearly, the Examiner has also stated that "Franz does not disclose that the NSAID and misoprostol used are tablets.". Applicant presumes the Examiner means that Franz does not disclose that the NSAID and misoprostol used are used as separate tablets. Applicant agrees. Franz teaches that all of the drug in the composition is in the drug release layer.

But The Examiner has, respectfully again, as with the prior rejection of Sims, in view of Kararli in further view of '321, misapplied and misread Stuerzebecher teachings with regard to the term "granule" as rendering the term "tablet" obvious to one skilled in the art for the same reasons set out above . This is simply not the case. Even if the Examiner's alleged combination were made respectfully there would not be two smaller tablets in a pharmaceutical tablet since at best '321 teaches a prostaglandin and a thromboxane receptor antagonist suitable for joint application to thrombotic and thromboembolic syndromes, meaning simultaneous but separate administration or combined in a dose unit. In this regard please see column 2 line 31 to 35 of '321. Since neither Franz nor '321 teach two separate smaller tablets in a pharmaceutical tablet even if the term "granules" were read in the manner alleged by the Examiner, and for the reasons set out above this is clearly not the case, one would still not arrive at Applicant's teaching and Claim 1 as follows:

> A **pharmaceutical tablet** comprising a shell in which is imbedded **two smaller tablets** covered by the material of the shell of the pharmaceutical tablet, **one of which smaller tablets comprises an** NSAID and **the other of which smaller tablets comprises misoprostol,** whereby the two smaller tablets are not exposed to the environment [of] at the surface of the pharmaceutical tablet , being protected by said shell.(emphasis added)

This is again supported by the Declaration of Dr. Lipp for example at the paragraphs indicated as follows:

> ***At paragraph 57*** *As I describe further below, I also disagree with the examiners conclusions regarding the combined teachings of the '704 and '321 patents. In my opinion, these two patents, read alone or in combination, do not render the inventions of the '142 patent obvious. Further, it is also my opinion that these two patents (i) also teach away from each other and thus should not be read together and (ii) teach away from the inventions of the '142 patent application. Thus, I would not expect that a skilled formulator would have been motivated to follow the combined teachings of these two patents when trying to develop a stabilized combination tablet formulation containing a NSAID and misoprostol.*

Again respectfully the Examiner is attempting to create a 20/20 hindsight reconstruction but has fallen well short in doing so.

In Re: Fritch, 23 U.S.P.Q. 2d 1780 (Fed. Cir. 1992)

> *"Wilson and Hendrix fail to suggest any motivation for, or desirability of, the changes espoused by the Examiner and endorsed by the Board. Here, the Examiner relied upon hindsight to arrive at the determination of obviousness.* ***It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious*** *(emphasis added). The court has previously stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."*

In Re: Rouffet, 47 U.S.P.Q. 2d 1453 (Fed. Cir. 1998)

> *To prevent the use of hindsight based on the invention to defeat patentability of the invention,* ***this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.*** (emphasis added)

Referring to the traditional test in Graham and John Deere, Applicant has assessed the scope and content of the prior art cited by the Examiner and set out the differences between the prior art and the claims at issue. Clearly, none of the prior art references alone or in any combination addresses the problem of environmental degradation of the prostaglandin as does Applicant's invention in the manner as contained in amended claim 1. Claim 1-11 are therefore patentable in view of the fact that the specific combination set out above in amended claim 1 is not disclosed in the prior art and is not obvious to one of ordinary skill in the art from the teachings the prior art cited by the Examiner.

Referring to the In Re Semaker Decision before the Court of Appeals, Federal Circuit 702 F 2d 989, 217 USPQ 1 it was stated therein;

> "When one skilled in the art at the time of the invention is considering all the prior art in combination, we wholly fail to perceive what more he would have found. The most that would have appeared to have been suggested was the use of transfer prints on rough substrates by which, no doubt, a variety of designs might have been achieved. Mating or registering are suggested nowhere in the prior art. Therefore, it does not show how to approach the results this inventor achieved. No prior art suggests expressly or by implication keeping the print off the substrate and providing a "sculptured" embroidery in a pattern to mate and register with the print."...

> "The lesson of this case appears to be that prior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings. It does not appear from the opinion that the inventor actually did anything not disclosed somewhere in the prior art references, and in that regard the case was less favorable for unobviousness than the case at bar, where none of the prior art references disclosed an embroidery inserted between the print and the substrate, "registered" or mated the print with the embroidery, not the substrate, and transferred the print to the insert, not to the substrate."

Following the Re: Sernacker reasoning as well, Applicant's invention is not suggested directly or indirectly from any combination of the prior art since the prior art does not teach that the prostaglandin be contained in a smaller tablet and that the NSAID be contained in a smaller tablet; and both tablets subsequently being contained in a pharmaceutical tablet. The advantages of doing so for the prostaglandin and the NSAID is that the degradation issues set out in the background of Applicant's invention, and in Gimet are clearly addressed by Applicant's improved pharmaceutical tablet heretofore left unaddressed in their entirety by Franz and '321 or Sims, Kararli and '321 and in any combination thereof. Applicant's invention therefore achieves more than any combination of the prior art cited by the Examiner and is clearly patentable. There is no motivation within any of reference absent Applicant's invention and the teaching thereof to arrive at Applicant's combination. In fact, Applicant submits that Franz and '321 or Sims, Kararli and '321 could not easily be combined and they are to a certain degree mutually exclusive since they in fact teach in opposite directions with respect to the provision of the misoprostol and the NSAID being in one layer in one case, that is Franz, or '321. Clearly, there is no suggestion therefore in either reference that the compositions could be combined in the manner alleged by the Examiner. The prior art does not suggest the desirability of making such a combination. There is no motivation in the prior art to do so.

The Examiner is referred to in Re: Regal in this regard wherein it states,

> *"There must be some logical reason apparent from positive concrete evidence of record which justifies a combination of primary and secondary references."*

Clearly therefore, Applicant has amended the claims to overcome the Examiner's alleged obviousness rejections and has provided expert evidence in the form of the Declaration of Dr.

Michael Lipp to support the arguments made herein to refute the Examiner's position in full and it is requested that full reconsideration be given to the claim amendments and Applicant's arguments.

One of the benefits of Applicant's invention is that it overcomes the problem that misoprostol is highly unstable and it is thus desirable not to have the misoprostol and the NSAID mixed together so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol. Applicant refers to the Gimet patent, U.S. Patent 5,601,843, at page 2, line 5 of the Disclosure as one solution. Applicant states however that the difficulty with Gimet is that the misoprostol is disbursed throughout the mantle and is thus exposed to the environment of the surface of the tablet. This exposure increases the vulnerability of the misoprostol to degradation due to the effects of light or atmospheric oxygen and moisture.

In view of the above submissions neither Franz in view of '321 nor Sims, in view of Kararli in further view of '321 teach Applicant's invention and further that no combination nor any one of the references teaches Applicant's invention as set out in claim 1 above. This conclusion was reached by Dr. Lipp as well as exemplified by the following paragraphs of his declaration:

At paragraph 64 *Thus, it is my opinion that neither the combinations of the '507, '321 and '939 or the '704 and '321 teach towards or disclose the claimed inventions of the '142 patent application. As a result, I disagree with the statements made and conclusions reached by the examiner with respect to these points as described above. Further, it is also my opinion that these patents teach away from the inventions of the '142 patent application and in part teach away from each other as I have indicated above.*

At paragraph 57 *As I describe further below, I also disagree with the examiners conclusions regarding the combined teachings of the '704 and '321 patents. In my opinion, these two patents, read alone or in combination, do not render the inventions of the '142 patent obvious. Further, it is also my opinion that these two patents (i) also teach away from each other and thus should not be read together and (ii) teach away from the inventions of the '142 patent application. Thus, I would not expect that a skilled formulator would have been motivated to follow the combined teachings of these two*

patents when trying to develop a stabilized combination tablet formulation containing a NSAID and misoprostol.

Full reconsideration of the claim set 1-11 is therefore respectfully requested for the reasons set out above. The Examiner is also referred to the prior Response submitted June 18, 2003 including various attachments the contents of said response and attachments being incorporated by reference in its entirety.

Applicant encloses a cheque in the amount of $1,720.00 USD which consists of $950.00 for the Three Month Extension of Time, and $770.00 for filing the Request for Continued Examination (RCE). If there is any deficiency or surplusage of the fees enclosed for the above-mentioned application, please obtain any such deficiency or credit the surplusage to Deposit Account 08-3255 and advise Applicants' Agent.

If the Examiner has any questions or requires further information, he is respectfully requested to contact Applicants' Agent, Neil H. Hughes at (905) 771-6414 collect at his convenience.

Respectfully submitted,

Neil H. Hughes, P.Eng.
Registration No. 33,636
Agent for Applicant

NHH:jlh
Enclosures:
1) Request for Continued Examination (RCE) Transmittal Form
2) Extension of Time;
3) Notarized Declaration of Dr. Michael Lipp with Exhibits;
4) Cheque in the amount of $1,720.00 USD